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Award Number: DAMD-17-03-1-0236

TITLE: Prostate Cancer Mortality and Herbicide Exposure in Vietnam Veterans

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REPORT DATE: April 2005

TYPE OF REPORT: Annual

PREPARED FOR: U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

DISTRIBUTION STATEMENT: Approved for Public Release;
Distribution Unlimited

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. REPORT DATE	2. REPORT TYPE	3. DATES COVERED
01-04-2005	Annual	1 Apr 2004 –31 Mar 2005

4. TITLE AND SUBTITLE

Prostate Cancer Mortality and Herbicide Exposure in Vietnam Veterans

5a. CONTRACT NUMBER

5b. GRANT NUMBER
DAMD17-03-1-0236

5c. PROGRAM ELEMENT NUMBER

6. AUTHOR(S)

Steven D. Stellman, Ph.D.

5d. PROJECT NUMBER

5e. TASK NUMBER

5f. WORK UNIT NUMBER

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)

Columbia University
New York, NY 10025

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
U.S. Army Medical Research and Materiel Command
Fort Detrick, Maryland 21702-5012

10. SPONSOR/MONITOR'S ACRONYM(S)

11. SPONSOR/MONITOR'S REPORT NUMBER(S)

12. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for Public Release; Distribution Unlimited

13. SUPPLEMENTARY NOTES

14. ABSTRACT The association between exposure to military herbicides and subsequent death from prostate cancer will be investigated in a cohort of approx. 100,000 Vietnam veterans who applied to the Agent Orange Veteran Payment Program (AOVPP), 1985-1994. Exposure opportunity will be assessed via a geographical information system (GIS) and herbicide and troop location databases previously developed by the investigators. Cause of death will be ascertained via National Death Index (NDI) searches. Epidemiological analyses will include comparison of age-specific prostate cancer death rates, proportional mortality ratios (PMR), standardized mortality ratios (SMR), and proportional hazards methods, using unexposed veterans as a reference population. **RESULTS.** NDI queries yielded causes of death for claimants who had died by 12 December 1999. Overall mortality was elevated for malignancies which the Institute of Medicine deemed "sufficient evidence" of association with herbicides. Microfilm record abstraction of military unit histories is complete for prostate cancer cases and controls and in progress for comparison cancers. Exposure assessments in progress are the basis for studies of prostate cancer risk in relation to exposure to dioxin-contaminated phenoxy and other herbicides in Vietnam.

15. SUBJECT TERMS
prostate cancer, Vietnam veterans, Agent Orange, herbicides, dioxin

16. SECURITY CLASSIFICATION OF:			17. LIMITATION OF ABSTRACT	18. NUMBER OF PAGES	19a. NAME OF RESPONSIBLE PERSON
					USAMRMC
a. REPORT	b. ABSTRACT	c. THIS PAGE			19b. TELEPHONE NUMBER *(include area code)*
U	U	U	UU	19	

Table of Contents

INTRODUCTION

Prostate cancer is the most common cancer diagnosed among males in the US and other Western countries[1], yet little is known about its causes. Elevated prostate cancer risks have been associated with occupational exposure to phenoxy herbicides and other agricultural chemicals[2,3]. One large group of men who may be at increased risk from exposure to phenoxy herbicides consists of veterans of the Vietnam War (1962-1975), during which the US military sprayed over 19 million gallons of phenoxy and other herbicides in the Republic of Vietnam (RVN). Many of the 3.2 million servicemen stationed in RVN were assigned to military duties which involved exposure to these herbicides and to 2,3,7,8-tetrachloro-*p*-dibenzodioxin (TCDD or dioxin), a carcinogenic contaminant of Agent Orange.[4] An expert Committee of the Institute of Medicine (IOM) concluded that there is "limited/suggestive evidence" of association with prostate cancer.[5,6,7,8] but this conclusion is based on studies of non-veteran populations, or on very small veteran studies.[9] The purpose of this study is to evaluate the association between exposure to military herbicides and subsequent prostate cancer mortality in a cohort of about 100,000 claimants to the Agent Orange Veteran Payment Program (AOVPP). The AOVPP was created by the Eastern US Federal District Court (New York) to administer the settlement of a class-action lawsuit of veterans against chemical manufacturers. Fact and cause of death among the 26,000 expected deaths in this cohort are being ascertained via Social Security and National Death Index searches. Exposure is being assessed from military records abstracted from the extensive AOVPP microfilm files, using our geographic information system (GIS) database of military unit locations throughout the War, and an exposure assessment methodology that we developed under a contract from the National Academy of Sciences.[10,11] Measures of association include comparisons of age-specific rates with unexposed veterans and the general population, and comparison of proportional mortality ratios, standardized mortality ratios, and odds ratios generated from proportional hazards models among subgroups with different estimated levels of exposure opportunity.

BODY

The overall project tasks outlined in the approved Statement of Work (SOW) are shown in Table 1, below.

Table 1. Statement of Work Tasks and Status

***Task 1.* To obtain the causes of death for known decedents.**	**Status**
a. Initiate application process for National Death Index and vital status searches.	Completed
b. Obtain cause-of-death file for known decedents from National Death Index NDI-Plus and incorporate into AOVPP database; resolve ambiguities.	Completed
c. Obtain vital status for applicants who were alive at time of filing claims.	Completed
d. Obtain cause-of-death data from NDI-Plus for approximately 10,000 applicants reported deceased in vital status searches.	Completed

***Task 2.* To obtain Agent Orange Exposure Opportunity Scores for AOVPP cohort members**	**Status**
a. Code military unit with UIC code based upon information in microfilm copy of military records.	Complete for prostate cancer In progress for comparison cancers (soft-tissue sarcoma, CLL, AML)
b. Refer to primary reference matter for supplementary military history data.	Months 1-6 of no-cost extension period
c. Use GIS to obtain Exposure Opportunity Scores from UICs.	Months 4-8 of no-cost extension period

***Task 3.* To analyze mortality rates in relation to Agent Orange exposure scores and develop final report**	**Status**
a. Overall and disease-specific mortality analysis of cohort Proportional mortality ratios (PMR) Standardized mortality ratios (SMR)	Complete
b. Mortality in relation to exposure	Months 9-12 of no-cost extension period

Synopsis. During Project Year 1 (01 April 2003 to 31 March 2004) most of **Task 1** was completed, as will be described. Project Year 2 (01 April 2004 to 31 March 2005) was devoted primarily to completing **Task 1**, to accomplishing much of **Task 2** including developing and testing software tools, and to beginning **Task 3**, which will be completed during the approved no-cost extension period (01 April 2005 to 31 March 2006).

The body of this Year 2 Annual Report is in five sections. The first four summarize progress for major project functions, while the last outlines the remaining tasks.

Section 1. Vital Status and Cause of Death Ascertainment
Section 2. Selection of cases and controls for nested case-control study
Section 3. Exposure Assessment
Section 4. Data Analysis
Section 5. Remaining Tasks

Section 1. Vital Status and Cause of Death Ascertainment

The study population consists of approximately 16,000 deceased veterans on whose behalf claims to the AOVPP were filed by survivors, and an additional 85,000 veterans who filed claims while still alive. Cause of death information was obtained for the decedent population during Year 1 via National Death Index searches. Matches were obtained for 15, 962 veterans. As noted in the Year 1 Annual Report, extensive quality assurance testing was done to assure ourselves that the death records were obtained for the right veterans. Also in Year 1, vital status searches were made to ascertain which of the non-deceased veterans had died subsequent to filing his AOVPP application. A total of 14,683 veterans who had died were identified in this manner.

On 2 April, 2004, we submitted to the National Death Index the records of 9,805 veterans who had died subsequent to filing. We limited the submission to veterans who had died on or before 31 December, 1999, in order to remain within the budgetary limits of the contract. We intend to seek additional funding to determine causes of death for the remaining 4,878 veterans who died after 1999. Matches were found for 9,743 veterans.

New York City cause of death submission. Due an unusual provision of the New York City Health Code, special procedures are required to obtain cause of death information from the National Death Index for persons dying in New York City. These procedures require notarized privacy assurances from the administration of the requestor's organization. We met the requirements and submitted a formal request to New York City on 24 November, 2004. Our request was approved by NYC on 21 December, 2004. On 11 January, 2005, we requested that NDI process 368 NYC deaths. The results were returned to us on 18 January, 2005.

The final cohort consists of all applicants to the Agent Orange Veteran Payment Program who were active duty members of the US Armed Forces between 28 February 1961 and 7 May, 1975, and who were discharged alive and were alive on 1 January 1, 1979, subject to follow-up date restrictions noted above. A further restriction was that deceased veterans on whose behalf claims were filed by survivors were excluded from the cohort if the cause of death was not from "natural causes," i.e., accident, homicide, or suicide, because these individuals were automatically ineligible for compensation. Finally, we created an analysis dataset for preliminary mortality studies which restricted deaths to those occurring through 31 December 1998, the last day on which the ICD-9 coding system was in use. We did this in order to avoid having to deal with minor incompatibilities with the ICD-10 system which went into effect 1 January 1999 during exploratory analyses. We have since developed a comprehensive conversion table for the two systems, and will utilize all reported deaths in planned analyses.

The breakdown of veterans in the analysis dataset is shown in Table 2.

Table 2a. Vital status of all claimants at time of filing of claim

Vital status at time of filing	No. of claimants
Deceased	15,962
Alive	84,910

Table 2b. Vital status of claimants who filed while still alive, as of 31 December, 1998

Vital status on 31 December, 1998	No. of claimants
Deceased	7,633
Alive	77,277
Total	84,910

Section 2. Selection of Cases and Controls for Nested Case-Control Study

A major analytical goal is estimation of relative risks for prostate cancer in relation to herbicide exposure. Because of the effort required to extract from the microfilm archives the military records needed for exposure, it is not practical to do an exposure assessment for the entire cohort. Instead, we planned a nested case-control study using all prostate cancer cases, with a sample of controls from each of the sub-cohorts used as the comparison groups.

An important principle of control selection in case-control studies is to avoid choosing as controls persons with diseases potentially related to the exposure under study[12]. We took as a guide to potentially related diseases the Institute of Medicine's listings in its biennial reviews of health effects of Agent Orange,[13] specifically those disease which the IOM regards as having "Sufficient Evidence" of an association as well as those for which "Limited/Suggestive Evidence" exists. The "Sufficient Evidence" category includes soft-tissue sarcoma, chronic lymphocytic leukemia, Hodgkin disease, and non-Hodgkin's lymphoma. The latter category includes prostate and respiratory cancers, multiple myeloma, and diabetes.

After the causes of death were known from the NDI results, we extracted controls from the pool of claimants not dying from the above diseases. We used a ratio of five controls per case, frequency matched on year of birth and state of residence (or residence of payee if that of veteran was not available.) We used this relatively high control:case matching ratio in order to make allowances for veterans with missing or incomplete records. With experience we found that approximately 24% of veterans fell in this category: 12% had only partial data, 8% had no usable data, and 4% were ineligible.

To provide an essential context for case-control analyses by enabling studies of potential cause-specific biases, as well as to have a basis for comparison of risks, we decided to do case-control analyses for several cancers in addition to prostate. We selected soft-tissue sarcoma (STS), chronic lymphocytic leukemia (CLL), and acute myelogenous leukemia (AML). STS and CLL, but not AML, are in the IOM "Sufficient Evidence" category. An elevated risk for CLL but not for AML, would argue against a bias towards finding an association for leukemia in general. It would also reduce concern that a positive finding for prostate cancer might be due to

disproportionate self-selection of individuals with cancer in general. A separate set of controls was chosen for each of those diseases.

Section 3. Exposure Assessment

The exposure metrics used in this study are a set of exposure opportunity indexes (EOIs) which we previously developed and validated under a contract from the National Academy of Sciences. The concepts and methods have been published[10,11]. To summarize, we developed a geographic information system (GIS) for Vietnam, whose layers include databases of all known herbicide spraying (the so-called HERBS file, which we extensively cleaned and edited[4]) as well as other types of military and civilian facilities. We have also developed an extensive set of location history databases for military units. Exposure assessment for an individual cohort member consists of the following steps:

1. Extract his military records from the AOVPP microfilm archives
2. Code his military unit history and military occupation specialties for each unit in which he served during his tour or tours of duty in Vietnam
3. Create a chronological list of unit location records (the "location history) by referencing the unit location databases
4. Apply our EOI algorithms[10] to his location history records to obtain a set of exposure metrics (direct hits within 0.5 km, 1 km, 2 km, 5 km, and E4 score weighted by time and distance).

Step 1: Extract military records. This process was described in the Year 1 Annual Report, pp. 13-15. It is a highly labor-intensive procedure which involves locating military records within a microfilm archives consisting of 860 reels of 35-mm microfilm. The process has been automated to the extent possible using Microsoft Access in conjunction with a Minolta MS-6000 scanner, and has been optimized by programming the Access database to prompt for cartridges and frames in physical rather than social security number order. Since AOVPP documents were filmed in the order received, and because military records were often obtained and filmed after the original application packet was submitted, many individuals' records are distributed among multiple reels. Therefore, a veteran's file may remain open for many months until his last document is finally retrieved. Software was developed to periodically scan the document image database to identify veterans with completed image sets by comparing their image sets with the master microfilm index. These complete image sets were automatically placed in unique folders to be transmitted to the military records specialist for coding.

Because of the immense effort required, it was never contemplated that coding for exposure assessment could be done for the entire cohort of over 100,000 veterans. Rather, coding effort was directed to the target cases (prostate cancer and certain other diseases chosen for comparison – see Section 2 above). However, this targeted coding could not commence until we knew the identities of the cases and controls, which had to await receipt of the results of the first NDI submission. This accounts in part for the delay in the overall project schedule. All available military records for prostate cancer cases and associated controls have now been extracted, covering 235 cases and 1,149 controls.

Table 3 breaks down the data found to be available within the microfilm archives for prostate cancer cases and controls. A small percentage (3.0%) was found to be ineligible upon

inspection of their military records, while nearly one-tenth had no usable data. We project that all prostate cancer coding will have been completed by the end of the second month of the no-cost extension period.

In all, we identified 7,127 documents in the microfilm archives potentially relevant to assessment of exposure in the 1,384 prostate cancer cases and associated controls. All documents were retrieved and reviewed, and 6,065 were scanned as pdf image files (on examination the remainder was deemed not relevant to exposure, blank, of poor quality, or for the wrong veteran). For veterans with at least one document on file, an average of 5.15 documents was identified and an average of 4.42 was scanned.

Table 3. Numbers of cases and controls ascertained for nested prostate cancer case-control study

	Cases	Controls	Total	Percent
All Vietnam tour records available	140	739	879	63.5
Partial Vietnam tour records only	30	135	165	11.9
No usable data	21	110	131	9.5
Ineligible	12	29	41	3.0
Done	203	1013	1216	87.9
Not done - awaiting coding	32	136	168	12.1
Total SSNs	**235**	**1149**	**1384**	**100.0**

The breakdown of military record abstractions for the three comparison causes is given in Table 4.

Table 4. Numbers of cases and controls available for studies of three cancers: STS, CLL, AML

	Cases	Controls	Total	Military record abstraction complete	Percent
Soft tissue sarcoma	218	1071	1289	722	56.0
Chronic lymphocytic leukemia	119	575	694	394	56.8
Acute myelogenous leukemia	219	1085	1304	654	50.2

Step 2: Code military unit history. Unit history coding is done by Ms. Francine Benjamin, the military records specialist, and is usually complete within a few weeks of the scanning work, so there is no backlog. Veterans have been coded to over 2,500 distinct military units. The median start date for the first tour of duty was 30 December, 1967. The distribution of first-tour start dates is shown in Figure 1 below and illustrates that the great proportion of veterans were stationed in Vietnam during the peak years of herbicide spraying.

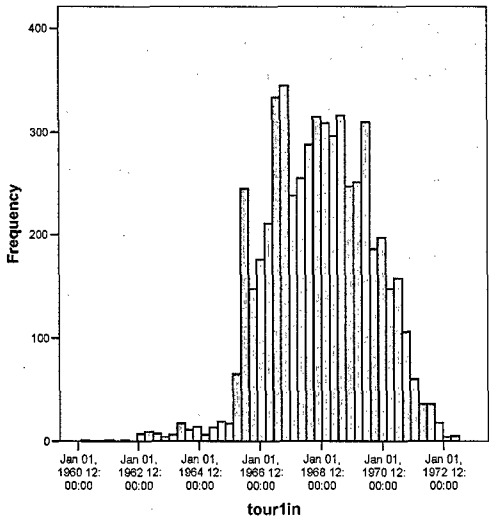

Figure 1. Frequency distribution of first tour of duty

Step 3. Create a chronological list of unit location records (the "location history) by referencing the unit location databases. Software – "Location History Generator" – was developed to extract all available unit history data from the unit coding database and re-format it as a set of sequential records suitable for input to our exposure assessment program. An abbreviated input/output specification is shown below.

INPUT One or more records from the Form B database.

OUTPUT Two tables: Veteran information and Location history records.

Table A: Veteran information
SSN
Veteran name
Veteran date of birth
Number of tours of duty served
Number of units veteran served in
Data source: Records only, Exposure Information Form only, or both
Partial: Whether only a partial military history is available from records
Percent coverage = 100 x number of days for which location data exist in the unit location database divided by the total number of days in the veteran's service history

Table B: Location history records:
SSN
Tour number (1, 2, 3, etc.)
UIC number (1, 2, 3, etc.)
Day in
Day out
Latitude
Longitude

This step is currently under way and is expected to take up months 1-6 of the no-cost extension period.

Step 4. Apply our EOI algorithms[10] to his location history records to obtain a set of exposure metrics (direct hits within 0.5 km, 1 km, 2 km, 5 km, and E4 score weighted by time and distance).

This is the final step in preparing data for exposure analysis. The software – "Herbicide Exposure Assessment – Vietnam" – has been previously developed and validated and runs essentially instantaneously. Its input is the Table B output from the Location History Generator, and its output is a set of EOI metrics for each veteran. A pictorial diagram of the software is shown in Figure 2 below:

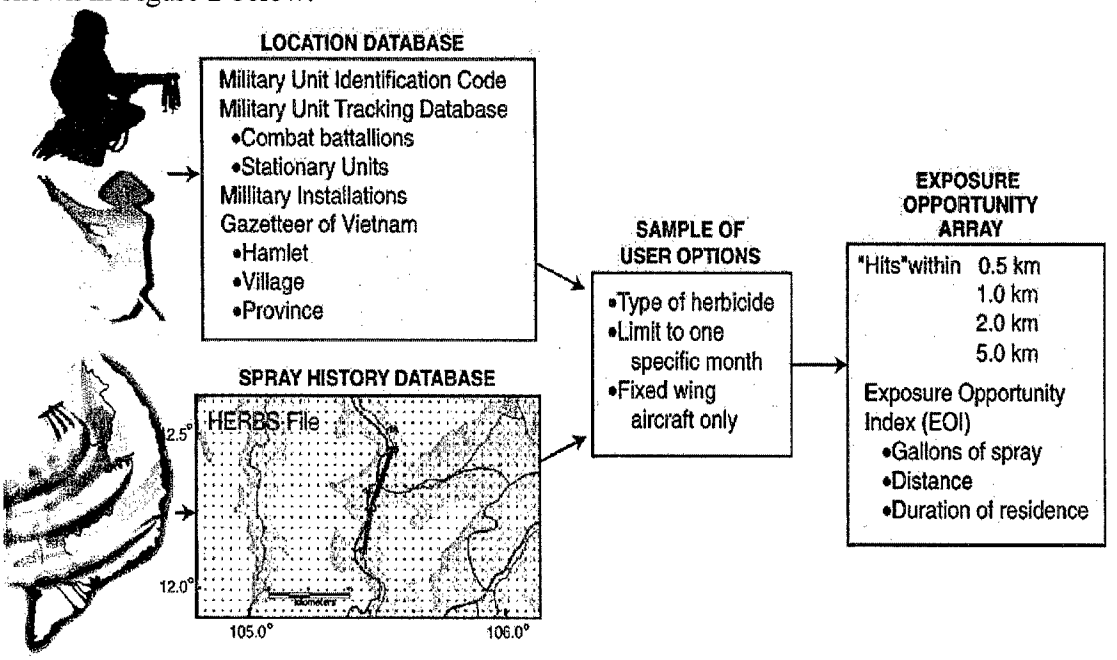

Figure 2. Schematic drawing of HEA-V software: Herbicide Exposure Assessment – Vietnam.

This step is contingent on results from Step 3. The actual calculations are virtually instantaneous.

Additional sources of exposure data.
We recognized that certain veterans may have held jobs in the military that involved exposure to herbicides, and that information about such exposures would be a useful if not essential adjunct to exposure opportunity score data. There are two potential sources of supplemental exposure data. First an Exposure Information Form was a mandatory part of each application packet. This form requested that the veteran provide military unit and tour data, as well as a checklist of more than 100 locations in Vietnam where large numbers of troops were known to have served. These data are used to corroborate data abstracted from the official military records, or may be used as a primary source when military records are missing or inadequate. The Exposure Information Form also contained an open-ended section where the veteran could provide in narrative form a description of his duties, particularly those which might have resulted in exposure to herbicides.

A second potential source of data on possible exposures is the military occupational specialty (MOS) which is recorded official records. This needs to be interpreted with caution, since a combat arms specialty such as "rifleman" may provide no clues as to possible exposure. However, there are a number of chemical specialties (e.g. 54F = chemical operations specialist) which might prompt a closer look at the military record itself.

Table 5 displays the 38 most common MOS codes, which cover 2,917 individuals. Three of the codes were not listed in any of the Vietnam-era listings used as code sources, and will require additional research to determine their designations.

Table 5. Most commonly found military occupational specialty codes

MOS	No. claimants	Meaning of code
11B	750	Infantryman
0311	172	Rifleman
94B	166	Food Service Specialist
11C	124	Indirect Fire Infantryman
13A	121	Field Artillery Basic
91B	112	Medical Specialist
12B	82	Combat Engineer
STUDENT	79	Student
13B	77	Cannon Crewman
63C	73	Track Vehicle Mechanic
63B	71	Power Generation and Wheel Vehicle Mechanic
76Y	71	Unit Supply Specialist
64B	69	Heavy Vehicle Driver
95B	69	Military Police
67N	63	Utility Helicopter Repairer
11D	57	Armor Reconnaissance Specialist
36K	52	Tactical Wire Operations Specialist
11E	52	Armor Crewman
71H	49	Personnel Specialist
64A	48	Light Vehicle Driver
11F	44	Infantry Operations And Intelligence Specialist
62E	40	Heavy Construction Equipment Operator
64C	38	Motor Transport Operator
36C	35	Wire Systems Installer/Operator
31M	34	Multichannel Communications Equipment Operator
3531	34	Unknown code
62B	33	Construction Equipment Repairer
76P	32	Stock Control Specialist
71B	31	Clerk-Typist
12A	30	Pioneer (engineer)
2531	29	Unknown code
72B	28	Communications Center Specialist
05C	28	Radio Teletype Operator
1371	25	Unknown code
11H	25	Heavy Antiarmor Weapon Crewman
76K	25	General Supply Specialist
13E	25	Cannon Fire Direction Specialist
67U	24	Medium Helicopter Repairer

Section 4. Data Analysis

Task 3. To analyze mortality rates and risks in relation to Agent Orange exposure scores and develop final report.

This task was broken into two segments. First, as soon as the mortality data from the National Death Index searches were available, we began a systematic study of death rates and risks in the population as a whole, without regard to exposure (which was not yet available). Much of this work is completed and will be described below. The second segment is the analysis of the case-control data using herbicide exposure as a primary variable. We will begin this phase as soon as exposure data become available.

1. Cohort mortality studies. We sought to characterize the mortality patterns in comparison to the general US population. An important aim was to see whether there was an elevated risk for illnesses for which the Institute of Medicine has concluded that there is "sufficient evidence" for an association with herbicide exposure, and to do the same for those illnesses for which it concluded "limited/suggestive evidence" exists.

We used Life Table Analysis Software (LTAS) distributed by the National Institute of Occupational Safety and Health, because it has built-in rate tables for most of the diseases of interest. Risks are reported by LTAS in the form of either standardized mortality ratios (SMRs) or proportional mortality ratios (PMRs), each with 95% confidence intervals. PMRs are easily converted to PCMRs using the method of Breslow and Day[14]. For diseases not covered by LTAS (histology-specific leukemias), and as a check, we computed an independent set of rates, using our observed deaths as numerators and official population figures as denominators. We calculated SMRs and PCMRs using standard statistical and life table methods[14].

Acquisition of population databases. We obtained mortality detail files for every year from 1966 through 2001 from the Office of Analysis and Epidemiology, National Center for Health Statistics. The CD's for 1966-1988 are public use files and were sent to us immediately upon request. Files for later years are subject to approval. On 28 June, 2004, we filed the appropriate applications for Compressed Mortality Files for 1989-98 and for 1999-2001. The requests were approved and the CD's were sent soon thereafter.

The population of eligible veterans was treated as two separate cohorts for the purpose of analysis. The deceased cohort consists of those veterans who were deceased at the time of filing. Analysis of deaths in this cohort is limited to PCMR analysis[12]. Claimants who were alive when their claims were filed are termed the living cohort, and their deaths are studied using SMR methods. Approximately 40% of the living cohort were highly disabled when they filed their claims; it is well known that persons with severe disabilities have a considerably higher death rate than the general population[15]. This implies that population rates will underestimate mortality even if there is no impact of herbicide exposure. This is evidenced by an all-cause SMR of 1.93. To offset this potential bias we used the relative standard mortality ratio (RSMR), which is simply the cause-specific SMR divided by the SMR for the entire population[14]. While this does not remove the potential bias due to high baseline mortality rates (most causes were greater than in the general population), it does permit one to assess whether specific causes are elevated relative to each other and to benchmark causes such as coronary heart disease.

The SMR results for the living cohort are shown in Table 6 and the PCMR results for the deceased cohort are shown in Table 7. The causes of death which are designated "Sufficient" by the Institute of Medicine were elevated in both cohorts. Prostate cancer was elevated in the living cohort with an SMR of 1.78. However, its RSMR was 0.92 (95% confidence interval 0.72 – 1.12).

One shortcoming of the microfilm records is that they rarely contain information about the race or ethnic background of the participant. This makes it impossible to apply race-specific mortality rates. Since prostate cancer rates are higher in blacks than in whites, failure to adjust for race could lead to biased risk estimates. We examined this issue in a sensitivity analysis in which we used US Census data for 1990 to determine the racial makeup of the zip code in which the claimant had lived (or the payee if the claimant's address was not available). We repeated the mortality analyses using only those individuals who resided in a zip code which was either at least 90% white or 90% non-white, using US white and non-white death rates, respectively, as references, and obtained results which differed very little from those in Tables 6 and 7.

The mortality analysis methods which we use provide outcome data for all causes, not just those of primary interest to the parent study. It was of additional interest to determine whether other causes were also elevated, both as a way of probing potential selection biases as well as to gather data which may be of importance for veteran health in general. Noting recent recommendations of the Institute of Medicine regarding neurological diseases,[8] we examined mortality for two neurodegenerative diseases, amyotrophic lateral sclerosis (ALS) and multiple sclerosis (MS), both of which we found to be elevated. In the deceased cohort, the PMR for ALS was 1.23 (0.90 – 1.62) and for MS was 1.37 (1.00 – 1.80). In the living cohort the RSMR for ALS was 1.49 (.95 – 2.03) and for MS was 2.92 (1.98 – 3.86). These findings were reported at the 2005 meeting of the Society for Epidemiologic Research in Toronto.

2. Case-control analysis with exposure

As noted above, data abstraction for prostate cancer cases and controls is complete and exposure assessment is in progress. None of our preliminary calculations have yet taken exposure into account. Exposure-specific risk estimates will be carried out in months 9-12 of the no-cost extension year.

Section 5. Remaining Tasks

In the no-cost extension year we will complete the following tasks:

Task	Timetable, Year 03
Complete abstraction of military unit histories from microfilm archives for the comparison cancers (soft-tissue sarcoma, CLL, AML)	Months 1-6
Evaluate exposure opportunity indexes (EOIs) and examine other possible exposure indicators from archived records	Months 4-8
Estimation of risk for prostate and other cancers in relation to herbicide exposure	Months 9-12

Table 6. Standardized Mortality Ratios (SMRs) for selected causes among 84,010 disability claimants to the Agent Orange Veteran Payment Program, followed up 1989 – 1998.

IOM DESIGNATION[a]	CAUSE OF DEATH	OBSERVED DEATHS	EXPECTED DEATHS	SMR[b]	RELATIVE SMR	95% CONFIDENCE INTERVAL
Sufficient	Chronic lymphocytic leukemia	29	6.30	4.60	2.39	1.52 – 3.25
	Connective tissue cancer	40	8.75	4.57	2.37	1.63 – 3.10
	Non-Hodgkin lymphoma	219	49.53	4.42	2.29	1.99 – 2.59
	Hodgkin's disease	32	4.38	7.31	3.79	2.47 – 5.10
Limited/Suggestive	Prostate cancer	82	46.03	1.78	0.92	0.72 – 1.12
	Respiratory cancers[c]	756	385.88	1.96	1.02	0.94 – 1.09
	Multiple Myeloma	88	18.24	4.82	2.50	1.98 – 3.02
	Diabetes Mellitus	176	100.47	1.75	0.91	0.77 – 1.04
None	Esophageal cancer	71	41.63	1.71	0.88	0.68 – 1.09
	Stomach cancer	42	32.01	1.31	0.68	0.47 – 0.89
	Colorectal cancer	174	101.98	1.71	0.88	0.75 – 1.02
	Acute Myeloid Leukemia	22	12.13	1.81	0.94	0.55 – 1.33
	Heart disease[d]	1828	1133.54	1.61	0.84	0.80 – 0.87
	All Cancers	2330	1062.75	2.19	1.14	1.09 – 1.18
	All Deaths	7633	3964.25	1.93	1.00	-

[a] Sufficient = IOM category "Sufficient Evidence of an Association." Limited/Suggestive" = IOM category "Limited/Suggestive Evidence of an Association"

[b] Adjusted for age and calendar-year using US Males as reference

[c] IOM category is larynx, trachea, bronchus, and lung combined, ICD-9 codes 161-162

[d] ICD-9 codes 390-398, 402-404, 410-414, and 420-429. This grouping includes ischemic heart disease, rheumatic heart disease, hypertension with heart disease, and endocardial diseases.

Table 7. Proportional cancer mortality ratios (PCMRs) in the deceased cohort.

IOM Designation[a]	Cause of death	Observed Deaths	PCMR[b]	95% Confidence Interval.
Sufficient	Chronic Lymphocytic Leukemia	54	1.41	1.06 – 1.81
	Connective Tissue	149	1.39	1.18 – 1.63
	Non-Hodgkin's Lymphoma	742	1.55	1.44 – 1.67
	Hodgkin's Disease	173	1.49	1.28 – 1.72
Limited/Suggestive	Prostate Cancer	111	0.60	0.49 – 0.71
	Respiratory Cancers[c]	2840	0.94	0.90 – 0.97
	Multiple Myeloma	191	1.53	1.32 – 1.76
None	Esophagus	217	0.72	0.63 – 0.82
	Stomach	270	0.88	0.78 – 0.99
	Colorectal	709	0.86	0.80 – 0.92
	Acute Myeloid Leukemia	171	1.26	1.08 – 1.46

[a] Sufficient = IOM category "Sufficient Evidence of an Association." Limited/Suggestive" = IOM category "Limited/Suggestive Evidence of an Association"

[b] Adjusted for age and calendar-year using US Males as reference

[c] IOM category is larynx, trachea, bronchus, and lung combined, ICD-9 codes 161-162

KEY RESEARCH ACCOMPLISHMENTS

- Completed vital ascertainment of over 84,000 members of the living cohort through 1999
- Obtained causes of death for all 7,633 known decedents in the living cohort through the National Death Index, including special processing for those dying in New York City
- Identified 235 cases and 1,149 controls for nested prostate cancer case-control studies
- Identified 556 cases and 2,731 controls for comparison studies of soft-tissue sarcoma, chronic lymphocytic leukemia, and acute myelogenous leukemia
- Identified and examined 7,127 documents in the microfilm archives potentially relevant to prostate cancer case-control study
- Scanned, abstracted, and coded tours of duty and military units records from 6,065 documents in the prostate cancer case-control study and began records abstraction for comparison case-control studies
- Carried out standardized mortality analysis of living cohort
- Carried out proportional cancer mortality analysis of decedent cohort
- Carried out mortality analysis for amyotrophic lateral sclerosis and multiple sclerosis
- Began exposure assessment phase for nested case-control studies

REPORTABLE OUTCOMES

A manuscript is in preparation which presents the findings shown in Tables 6 and 7. A preliminary version of these data was presented at the 2005 joint meeting of the Society for Epidemiologic Research and the Canadian Society for Epidemiology and Biostatistics in Toronto. In addition to the cancer data shown in the Tables, we observed and reported increased proportional excesses for two neurodegenerative diseases: amyotrophic lateral sclerosis and multiple sclerosis, as described above.

Presentations – Society for Epidemiologic Research, Toronto, June 29, 2005

Cancer Mortality in a Cohort Of 100,000 Vietnam Veterans. S.D. Stellman, C. Tomasallo, J.M. Stellman

Neurodegenerative Disease Mortality in Vietnam Veterans Exposed to Phenoxy Herbicides. C.D. Tomasallo, S.D. Stellman, J.M. Stellman

CONCLUSIONS

The first year of this study was devoted to establishing procedures for efficient identification and abstraction of military and medical records from the large microfilm archives (860 reels, over 1.2 million documents), and to initiation of vital status ascertainment and cause of death determination.

In the second year vital status ascertainment was completed, the nested case-control studies of prostate cancer and several other comparison endpoints was begun, and preliminary mortality analyses were carried out for decedent veterans whose claims were filed by next of kin, and for veterans who filed claims while still alive. In both subcohorts we determined that four malignancies were elevated for which the Institute of Medicine determined that "sufficient evidence" of an association with herbicide exposure exists: soft-tissue sarcoma, non-Hodgkin lymphoma, Hodgkin disease, and chronic lymphocytic leukemia. We made a similar finding for multiple myeloma, whose evidence the IOM classifies as "suggestive/limited." Prostate cancer was significantly elevated in the living cohort (SMR = 1.78, 95% confidence interval 1.42 – 2.19), but was not significant after adjustment for overall cohort mortality (RSMR = 0.92; 0.72 – 1.12). We also found elevated mortality from ALS and MS.

Our preliminary findings are consistent with the conclusions of the Institute of Medicine regarding cancers associated with exposure to military herbicides in Vietnam, especially those such as Agent Orange which were contaminated with dioxin, at least for "sufficient evidence" cancers. For "limited/suggestive evidence" cancers, including prostate, overall mortality is not elevated. However, these preliminary studies do not yet take herbicide exposure into account. Exposure assessment is under way and will be completed during the no-cost extension Year 03, along with planned analyses of cancer risk in relation to exposure opportunity.

REFERENCES

[1] Hsing AW, Tsao L, Devesa SS. International trends in prostate cancer incidence and mortality. Int J Cancer 2000; 85:60-67.

[2] Blair A, Zahm SH. Cancer among farmers. Occup Med 1991; 6:335-354.

[3] van der Gulden JWJ, Kolk JJ, Verbeek ALM. Prostate cancer and work environment. Am J Occup Med 1992; 34:402-409.

[4] Stellman JM, Stellman SD, Christian R, Weber T, Tomasallo C. The extent and patterns of usage of Agent Orange and other herbicides in Vietnam. Nature 2003;422:681-7.

[5] Institute of Medicine 1994. Committee to Review the Health Effects in Vietnam Veterans of Exposure to Herbicides. Veterans and Agent Orange: Health Effects of Herbicides Used in Vietnam. Washington, DC: National Academy of Sciences Press.

[6] Institute of Medicine. 1996. Veterans and Agent Orange: Update. Washington, DC: National Academy of Sciences Press.

[7]Institute of Medicine. 1998. Veterans and Agent Orange: Update. Washington, DC: National Academy of Sciences Press.

[8]Institute of Medicine. 2001. Veterans and Agent Orange: Update 2000. Washington, DC: National Academy Press.

[9] Giri VN, Cassidy AE, Beebe-Dimmer J, Smith DC, Bock CH, Cooney KA. Association between Agent Orange and prostate cancer: a pilot case-control study. Urology. 2004 Apr;63(4):757-60; discussion 760-1.

[10] Stellman JM, Stellman SD, Weber T, Tomasallo C, Stellman AB, Christian R, Jr. A geographic information system for characterizing exposure to Agent Orange and other herbicides in Vietnam. Environ Health Perspect 2003;111:321-328.

[11] Stellman SD, Stellman JM. Exposure opportunity models for Agent Orange, dioxin, and other military herbicides used in Vietnam, 1961-1971. J. Expos. Analysis Environ. Epidemiol. 14: 354-362, 2004.

[12] Rothman KJ, Greenland S. Modern Epidemiology, 2nd Ed (1998). Philadelphia: Lippincott-Raven.

[13] Institute of Medicine. Veterans and Agent Orange: Update, 2002. Washington, DC: National Academies Press, 2003.

[14] Breslow N E, Day N E. Statistical Methods in Cancer Research, Volume II. The Design and Analysis of Cohort Studies (IARC Scientific Publications No. 82). Lyon, International Agency for Research on Cancer, 1987.

[15] Social Security Administration Office of Disability Programs. "Disability Evaluation Under Social Security." SSA Pub. No. 64-039. Washington, DC, January, 2005.